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4-Heptanol, 2,6-dimethyl-
(Diisobutyl Carbinol; CAS RN 108-82-7)
High Production Volume (HPV) Chemical
Challenge Test Plan and Data Review

Prepared for:

The Dow Chemical Company

Prepared by:

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**4-Heptanol, 2,6-dimethyl-
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Final Test Status

4-Heptanol, 2,6-dimethyl- (Diisobutyl Carbinol; CAS RN: 108-82-7)		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY		Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL AND CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.4	Vapor Pressure	Y	N	N	Y	N	Y	N
2.5	Partition Coefficient	Y	N	N	N	Y	Y	N
2.6	Water Solubility	Y	N	Y	Y	N	Y	N
ENVIRONMENTAL FATE AND PATHWAY								
3.1.1	Photodegradation	Y	N	N	N	Y	Y	N
3.1.2	Stability in Water	Y	N	N	Y	N	Y	N
3.3	Transport and Distribution	Y	N	N	N	Y	Y	N
3.5	Biodegradation	Y	Y	Y	N	N	Y	N
ECOTOXICITY								
4.1	Acute Toxicity to Fish	Y	Y	Y	N	N	Y	N
4.2	Toxicity to Daphnia	Y	Y	Y	N	N	Y	N
4.3	Acute Toxicity to Algae	Y	Y	Y	N	N	Y	N
TOXICITY								
5.1	Acute Toxicity	Y	N	N	Y	N	Y	N
5.4	Repeated Dose Toxicity	Y	Y	Y	N	N	Y	N
5.5	Genotoxicity <i>In Vitro</i> (Bacterial Test)	Y	Y	Y	N	N	Y	N
5.5	Genotoxicity <i>In Vitro</i> (Mammalian Cells)	Y	Y	Y	N	N	Y	N
5.8	Reproductive Toxicity	Y	Y	Y	N	N	Y	N
5.9	Development Toxicity / Teratogenicity	Y	Y	Y	N	N	Y	N

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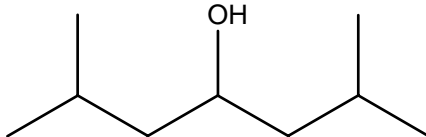
1.0 Introduction

This document provides a Test Plan and reviews the data availability for the High Production Volume (HPV) Chemical Challenge endpoints for 4-Heptanol, 2,6-Dimethyl-, hereafter called Diisobutyl Carbinol [DIBC; CAS RN 108-82-7]. DIBC is sponsored by The Dow Chemical Company.

2.0 General Use and Exposure

Diisobutyl Carbinol (DIBC) has a number of small volume uses. It is commonly used in mining, fabric softeners and textile and paper manufacturing. DIBC also is a lubricant additive intermediate, defoamer in adhesives, a coupling solvent for synthetic resins, a dispersing agent in coatings, and a chemical manufacturing processing solvent. Small amounts of DIBC are used in the fragrance industry as a chemical intermediate in the production of perfumes and/or flavors. Over 90% of the U.S. production of DIBC is as a chemical process solvent in the production of hydrogen peroxide. During 2002, 1 to 3 million pounds of DIBC were produced in the United States.

3.0 General Substance Information (Identity)

Chemical Name	4-Heptanol, 2,6-Dimethyl-
Synonyms	Diisobutyl Carbinol 2,6-Dimethyl heptanol-4 2,6-Dimethyl-4-heptanol 4-Heptanol, 2,6-dimethyl- 4-Hydroxy-2,6-dimethyl heptane Diisobutylcarbinol Nonyl alcohol, secondary sec-Nonyl alcohol
CAS Number	108-82-7
Structure	
Molecular Weight	144.26
Substance Type	Organic
Physical State	Liquid
Odor	Sweet
Purity	2,6-dimethyl-4-heptanol (DIBC) $\geq 70\%$ 4,6-dimethyl-2-heptanol (DMH) $\leq 30\%$ 2,6-dimethyl-4-heptanone $\leq 3\%$

4.0 Physical/Chemical Properties

A data summary for DIBC is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

4.1 Melting Point

The melting point for DIBC is listed as -65.2°C (DIPPR, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

4.2 Boiling Point

The boiling point for DIBC is listed as 177.9°C (DIPPR, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

4.3 Vapor Pressure

The vapor pressure for DIBC is listed as 0.260 hPa at 20°C (DIPPR, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

4.4 Partition Coefficient

The log K_{ow} for DIBC is predicted by EPIWIN to be 3.08 (U.S. EPA, 2000a). This value is consistent with the known properties of DIBC and is considered adequate to meet the HPV Chemical Challenge requirements.

4.5 Water Solubility

The water solubility value for DIBC was determined to be 570 mg/L (Wilson, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

5.0 Environmental Fate

A data summary for DIBC is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

5.1 Photodegradation

The model prediction for atmospheric photodegradation provides a second order rate of reaction with hydroxyl radicals of $18.7 \text{ E-}12 \text{ cm}^3/\text{molecule-sec}$ and a $t_{1/2}$ of 6.9 hours (U.S. EPA, 2000b). Because of the nature of use of DIBC, photodegradation is of minimal importance to the overall environmental fate. Rapid degradation from accidental release to the atmosphere, however, is anticipated based on the modeling. These data are considered adequate to meet the HPV Chemical Challenge requirements.

5.2 Stability in Water

DIBC does not react with water; the only functionality other than carbon-carbon and carbon-hydrogen bonds is the hydroxyl group, which does not hydrolyze.

5.3 Transport and Distribution

The Level III fugacity model (U.S. EPA, 2000c) was used to predict the distribution of DIBC released into the environment. Environmental exposure to DIBC is limited based on the use patterns as an industrial intermediate and solvent. For example, DIBC is not listed on the Toxic Release Inventory. Therefore, only accidental releases were considered for the fugacity modeling. Two scenarios, 100% release to air and 100% release to water were examined. For the air release, the model predicted a distribution of 90% into atmosphere, 8% into water, 2% into soil, and < 1% into sediment. For the water release, the model predicted a distribution of 1% into atmosphere, 97% into water, < 0.1% into soil, and 1% into sediment. These data are considered adequate to meet the HPV Chemical Challenge requirements.

5.4 Biodegradability

A study measuring the biodegradation of DIBC in an OECD 301F respirometer test under aerobic conditions for 28 days found that the DOC removal was 99.5% by Day 28; the ThOD reached 10% by Day 8 and 53% in the next 10 days, attaining 60% by Day 28. The author concluded that DIBC is not readily biodegradable because the strict criterion for the 10-day window was not met (Heim, 2003). DIBC can be classified as inherently biodegradable and nearly meets the criteria for ready biodegradation in this test system. These data are considered adequate to meet the HPV Chemical Challenge requirements.

6.0 Ecotoxicity

A data summary for DIBC is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

6.1 Toxicity to Fish

The 72- and 96-hour LC_{50} value for DIBC toxicity to freshwater fish (rainbow trout; *Oncorhynchus mykiss*) is reported as 28.6 mg/L (Marino and Yaroach, 2002a). The study was conducted in compliance with EPA OTS Guideline 797.1400 except that DIBC concentrations were not measured in the test solutions and nominal values were used throughout. Because DIBC does not hydrolyze, the nominal concentrations are acceptable and this LC_{50} value is considered adequate to meet the HPV Chemical Challenge requirements.

6.2 Toxicity to Aquatic Invertebrates

The 48-hour EC_{50} value for DIBC toxicity to *Daphnia magna* is 47.8 mg/L (Marino and Yaroach, 2002b). The study was conducted in compliance with EPA OTS Guideline 797.1300 except that DIBC concentrations were not measured in the test solutions and nominal values were used throughout. Because DIBC does not hydrolyze, the nominal concentrations are acceptable and this EC_{50} value is considered adequate to meet the HPV Chemical Challenge requirements.

6.3 Toxicity to Aquatic Plants

The 96-hour EC₅₀ values for DIBC toxicity based on biomass and growth rate to *Selenastrum capricornutum* (algae) are 7.41 and 29.95 mg/L, respectively (Roshon, 2002). The study was conducted in compliance with OECD Guideline 201. These data are considered adequate to meet the HPV Chemical Challenge requirements.

7.0 Human Health-Related Data

A data summary for DIBC is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

7.1 Acute Toxicity

The following acute toxicity data are available: acute oral LD₅₀ in rats = 3560 mg/kg bw; acute dermal LD₅₀ in rabbits = 4591 mg/kg bw; no deaths from an 8-hr exposure to substantially saturated vapor or cooled mist of DIBC (Carpenter, 1948). These data are considered adequate to meet the HPV Chemical Challenge requirements.

7.2 Repeated Dose Toxicity

A repeated dose toxicity study with reproductive and developmental screening was performed with DIBC according to the OECD Guideline 422 (Carney *et al.*, 2006). Crl:CD(SD) rats, 12/sex/group, were administered DIBC by gavage at dose levels of 0, 50, 150 or 500 mg/kg/day. Body weights and food consumption values were decreased for the females receiving 500 mg/kg/day of DIBC. Treatment-related increases in absolute liver weight were observed in the males of the mid (17%) and high dose (28%) groups as well as in the high dose females (10%). Corresponding increases in the relative liver weights were also identified in these groups. Microscopic observations of very slight hypertrophy of centrilobular hepatocytes in males in the 150 and 500 mg/kg/day groups and females in the 500 mg/kg/day group paralleled the increased liver weights. Increased relative kidney weights were observed in the 150 mg/kg/day females and the 500 mg/kg/day females and males, however, no clinical pathologic or histopathologic observations accompanied the increased weights. There was no evidence of systemic toxicity in the rats of either sex given 50 mg/kg/day. Therefore, the NOAEL for this study was considered to be 50 mg/kg/day based on the liver weight effects in the males and the kidney weight effects in the females at 150 mg/kg/day.

7.3 Genetic Toxicity (*in vitro*)

DIBC has been shown to be negative in a high quality Bacterial Reverse Mutation assay for *Salmonella* and *E. coli* strains with and without metabolic activation (Mecchi, 2002).

DIBC was tested in a cytogenetic assay (rat lymphocytes) according to OECD Guideline 473 at concentrations up to 1440 µg/ml without metabolic activation and up to 360 µg/ml with metabolic activation. DIBC was negative with and without metabolic activation in this assay (Linscombe *et al.*, 2004).

7.4 Reproductive and Developmental Toxicity

Male and female CD rats were dosed with DIBC at 0, 50, 150, or 500 mg/kg/day in a study conducted according to OECD Guideline 422 (see Section 7.2). There were no treatment-related effects at any dose on any of the reproductive parameters, pup survival indices or sex ratio. The NOEL for reproductive effects was 500 mg/kg/day, the highest dose tested (Carney *et al.*, 2006).

8.0 Conclusion

Adequate information is available for melting point, boiling point, vapor pressure, partition coefficient and water solubility for DIBC. Photodegradation and environmental distributions are adequately supported by the appropriate model data. DIBC does not have hydrolyzable groups and is stable in abiotic aqueous systems and is biodegradable. Aquatic toxicity data are available for fish, daphnia and algae indicating that DIBC is moderately toxic to aquatic organisms. DIBC is relatively non-toxic via acute oral, dermal and inhalation exposure. Following repeated dosing (OECD 422), minimal effects on liver weight and associated hepatocellular hypertrophy were observed as well as relative kidney weight increases. The NOAEL was 150 mg/kg/day. In bacterial and mammalian cell systems, DIBC is not mutagenic. In the OECD 422 study, DIBC did not affect reproduction at doses up to 500 mg/kg/day. The available data are considered adequate to meet the HPV Chemical Challenge Program requirements.

9.0 References

- Carney, E.W., C.L. Zabloutny, A.K. Andrus and K.E. Stebbins. 2006. Diisobutyl Carbinol (DIBC): A Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in CRL:CD(SD) Rats. Unpublished Report Number 051120 for The Dow Chemical Company by Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, USA.
- Carpenter, C.P. 1948. Range Finding Tests on Diisobutyl Carbinol. Unpublished Report Number 11-89. Mellon Institute of Industrial Research, University of Pittsburgh, PA, USA.
- DIPPR (The Design Institute for Physical Properties). 2000. The DIPPR Information and Data Evaluation Manager, Version 1.5.0, Copyright BYU-TPL2000.
- Heim, D. 2003. Diisobutyl carbinol: Determination of Ready Biodegradability Using the Respirometry Method. Unpublished Report (ABC No. 47679; Dow No. 020112) for The Dow Chemical Company by ABC Laboratories, Inc., Columbia, MO, USA.
- Linscombe, V.A., K.M. Jackson and M.R. Schisler. 2004. Evaluation of Diisobutyl Carbinol in an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes. Unpublished Report for Union Carbide Corporation by Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Danbury, CT, USA

Marino, T. A. and A. M. Yaroach. 2002a. Diisobutyl Carbinol: An Acute Toxicity Study with the Rainbow Trout, *Oncorhynchus mykiss* Walbaum. Unpublished Report (Dow No. 021047) for Union Carbide Corporation by Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, USA.

Marino, T. A. and A. M. Yaroach. 2002b. Diisobutyl Carbinol: An Acute Toxicity Study with the Daphnid, *Daphnia magna* Straus. Unpublished Report (Dow No. 021048) for Union Carbide Corporation by Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, USA.

Mecchi, M. S. 2002. *Salmonella* – *Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with Diisobutyl Carbinol. Unpublished Report (Covance Study No. 23500-0-422OECD; Dow No. 011222) for The Dow Chemical Company by Covance Laboratories Inc., Vienna, VA, USA.

Roshon, R. 2002. Diisobutyl Carbinol: Growth Inhibition Test with the Freshwater Green Alga, *Selenastrum capricornutum* Printz. Unpublished Report (ESG Study No. S2287; Dow No. 020026) for the Dow Chemical Company by ESG International Inc., Guelph, Ontario, Canada.

U.S. EPA (U.S. Environmental Protection Agency). 2000a. EPI Suite™, Version 3.10; KOWWIN Program, Version 1.66; PC-Computer software developed by EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC).

U.S. EPA (U.S. Environmental Protection Agency). 2000b. EPI Suite™, Version 3.10; AOPWIN Program, Version 1.90; PC-Computer software developed by EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC).

U.S. EPA (U.S. Environmental Protection Agency). 2000c. EPI Suite™, Version 3.10; Level III Fugacity Model; PC-Computer software developed by EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC).

Wilson, L. C. 2000. Liquid-Liquid Equilibrium Measurements for Eighteen Glycol Ethers, Ketones, Esters and Alcohols with Water. Project Report No. 44662, 10/13/2000. Union Carbide Corporation, S. Charleston, WV, USA.

Table 1: HPV Data Summary

4-Heptanol, 2,6-Dimethyl-
(Diisobutyl Carbinol; DIBC)

CAS RN: 108-82-7		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Handbook Data (DIPPR)	-65.2 °C
2.2	Boiling Point		Handbook Data (DIPPR)	177.9°C
2.3	Density		Handbook Data (DIPPR)	0.8112 g/cm ³ (at 20 °C)
2.4	Vapor Pressure		Handbook Data (DIPPR)	0.260 hPa (at 20 °C)
2.5	Partition Coefficient (log K _{ow})		KOWWIN v 1.66	3.08
2.6	Water Solubility		ASTM E 1148	570 mg/L (at 20 °C)
2.7	Flash Point		Handbook Data (DIPPR)	65.85 °C
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		AOPWIN v. 1.90	half-life: 6.9 hours (OH Rate Constant)
3.1.2	Stability in Water		Hydrolysis @ 25 °C	Does not react with water; the only functionality other than carbon-carbon and carbon-hydrogen bonds is the hydroxyl group which does not hydrolyze
3.3	Transport and Distribution		Mackay Level III 100% release to air;	90% into atmosphere, 8% into water, 2% into soil, < 1% into sediment
			Mackay Level III 100% release to water	1% into atmosphere, 97% into water, < 0.1% into soil, 1% into sediment
3.5	Biodegradation		OECD 301F	ThOD = 60% after 28 days
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	<i>Oncorhynchus mykiss</i>	OTS 797.1400	LC ₅₀ (96 hours) = 28.6 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates	<i>Daphnia magna</i>	OTS 797.1300	EC ₅₀ (48 hours) = 47.8 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	<i>Selenastrum capricornutum</i>	OECD Guideline 201	EC ₅₀ (96 hours) 7.41 mg/L (biomass) 29.95 mg/L (growth rate)

Table 1: HPV Data Summary

4-Heptanol, 2,6-Dimethyl-
(Diisobutyl Carbinol; DIBC)

CAS RN: 108-82-7		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat		LD50 : 3560 mg/kg bw
5.1.2	Acute Inhalation Toxicity	Rat		No deaths following 8-hr exposure to saturated vapor or cooled mist
5.1.3	Acute Dermal Toxicity	Rabbit		LD ₅₀ : 4591 mg/kg bw
5.4	Repeated Dose Toxicity	Rat	OECD 422	NOAEL = 150 mg/kg/day
5.5	Genetic Toxicity <i>In Vitro</i>			
	Bacterial Test (Gene mutation)	<i>S. typhimurium</i> and <i>E. coli</i>	OECD 471	Negative
	Chromosomal Aberration	CHO	OECD 473	Negative
5.8	Toxicity to Reproduction / Impairment of Fertility	Rat	OECD 422	NOAEL = 500 mg/kg/day (highest dose tested)
5.9	Developmental Toxicity / Teratogenicity	Rat	OECD 422	NOAEL = 500 mg/kg/day (highest dose tested)